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Perceptions of fecal microbiota transplantation for *Clostridium difficile* infection: factors that predict acceptance

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Abstract

Background Despite the effectiveness of fecal microbiota transplantation (FMT) for treating recurrent *Clostridium difficile* (*C. difficile*) infection, some patients are reluctant to accept this therapy. Our study examined attitudes towards FMT and factors that contribute to patients' acceptance of this treatment.

Methods We distributed patient surveys at a Veterans Affairs hospital, a public hospital, and an academic faculty practice. Multivariable logistic regression was performed, adjusting for factors associated with FMT acceptance on univariate analysis and prior experience with *C. difficile* infection.

Results Of 267 patients, only 12% knew of FMT prior to the survey, but 77% would undergo the procedure if medically indicated. On multivariable analysis, those with children and with college degrees or higher were more likely to agree to FMT (odds ratio [OR] 2.11, 95% confidence interval [CI] 1.02-4.35; OR 2.27, 95% CI 1.11-4.60 respectively). Sixty-five respondents (71%) chose colonoscopy as the preferred vehicle for FMT, while nasogastric tube was least preferred. Disease transmission was the most common concern (30%, n=242), and FMT success rate was the least selected concern (9.1%).

Conclusions Most patients in a diverse sample of gastroenterology clinics had no prior knowledge of FMT, but were receptive to the procedure. Having children and higher education levels were predictors for FMT acceptance. Our findings suggest that barriers to FMT utilization may be overcome with counseling about safety concerns. More data on the risk of transmitting diseases or clinical characteristics, such as obesity, through FMT are needed and will be important for the acceptance of this procedure.

Keywords Fecal microbiota transplantation, fecal transplant, FMT, patient perceptions, *Clostridium difficile*

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Conflict of Interest: None

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Introduction

Clostridium difficile (*C. difficile*) are spore-forming anaerobic bacteria [1]. Infection with toxigenic strains of this organism can cause a range of effects on its human hosts from asymptomatic carriage to life-threatening colitis. Although *C. difficile*-associated diarrhea (CDAD) was traditionally thought to primarily affect elderly, hospitalized, or chronically ill patients, the worldwide incidence of community-acquired CDAD has increased substantially in recent years [2-6]. CDAD can be transmitted not only by those with the illness, but probably also through asymptomatic carriers and environmental reservoirs [2]. Furthermore, there is a rising number of severe cases refractory to traditional antibiotic therapy, which has contributed to the increase

in *C. difficile*-related mortality [7-9]. In recent years, CDAD has become an increasingly common cause of hospitalization, contributing to the burden of rising healthcare costs [9,10].

Fifteen to thirty percent of CDAD patients who initially respond develop recurrent disease, and 65% of those patients are destined to develop more than one recurrence [11-13]. Therapies for recurrent CDAD include antibiotic tapers, pulsed antibiotic dosing, anion exchange resins, and administration of intravenous immunoglobulins or monoclonal antibodies; only limited data are available for all these therapies [14]. FMT is the latest treatment option for recurrent CDAD infections in patients who have previously failed traditional therapies, with a cure rate of approximately 90% [15,16]. During FMT, a liquid suspension of healthy donor stool is transplanted into an affected patient's gastrointestinal tract through nasogastric tube, enema, or colonoscopy. While the specific mechanism by which FMT treats CDAD is unknown, several studies have suggested that re-establishment of a diverse gut microbiome is key [17-19]. Other studies in mice and humans have shown that treatment with a limited number of gut bacteria can also cure CDAD, suggesting that transplantation of certain microbial functions, rather than merely diversity, is important [20-22].

There are now various case series and one randomized control study describing over 500 patients with resistant CDAD [23] treated with FMT [16]. While short-term adverse effects are limited [15,16], the long-term safety of FMT is still largely unknown. Notably, at the time of writing, the United States Food and Drug Administration has endorsed enforcement discretion for those providing FMT only for *C. difficile*-related indications, though there is no clinical indication for which FMT is currently FDA-approved [24].

As with any therapy, uptake of a new treatment modality depends not only on its efficacy, but also on physicians' and patients' perceptions of the therapy. Given the unsavory concept of administering donor stool into the colon of a recipient, patient and practitioner apprehension may constitute barriers to the uptake of FMT. Currently, only a few studies have examined the attitudes of the general patient population towards FMT. While these studies are important first steps in understanding the ultimate acceptance of this emerging therapy, the patients studied were limited to single medical centers, those who had already undergone FMT, or those considering FMT for non-CDAD indications [15,25,26]. Since the results of these studies may not reflect the attitudes of a broader patient population, we developed a survey to assess the interests and concerns regarding FMT for CDAD that was distributed to patients from varied ethnic and socioeconomic backgrounds. To our knowledge, this is the largest and most diverse study to examine patients' perceptions of FMT.

Materials and methods

Survey development

We designed a survey in the English language to evaluate perceptions of FMT and barriers to its recognition as an

acceptable therapeutic option (see Appendices). The survey included the following sections: 1) demographic data; 2) experience with complementary and alternative medications (CAM) and therapies; 3) personal medical history; 4) personal history of chronic diarrhea; 5) prior knowledge/experience of CDAD; 6) an introduction and description of FMT; and 7) an assessment of attitudes towards FMT and FMT delivery mode. The questions were geared toward discovering factors that may influence perceptions of FMT, in addition to general demographic data that may be predictive of acceptance of FMT.

Study participants and recruitment

Surveys were distributed over a 10-month period in the waiting areas of adult gastroenterology clinics of an urban public hospital (Bellevue Hospital Center), an urban Veterans Affairs hospital (New York Harbor Healthcare System-Manhattan Campus), and in faculty practices affiliated with New York University's Langone Medical Center, all located in New York City. Surveys were completed by and collected from patients waiting for their appointments. Participation was voluntary and anonymous; the participants were not compensated. Review board approval was waived at all 3 participating hospitals.

Statistical analysis

Statistical calculations were performed using STATATM 12.1 software (StataCorp). Unanswered questions were omitted from the analysis. Pearson χ^2 analysis was used to evaluate univariate factors associated with FMT acceptance. Factors that accounted for FMT acceptability with $P < 0.10$ on univariate analysis were analyzed by multivariable logistic regression. In addition, the existence of either first- or second-hand experience with *C. difficile* infection was also included in our model, given its presumed influence on FMT acceptability. For all analyses, a P -value < 0.05 was considered statistically significant.

Results

A total of 267 adult patients were surveyed across all clinical sites (Table 1). Overall, 12% (29/234) of respondents were aware of FMT prior to the survey and 77% (163/213) of all of the subjects would undergo the procedure if medically indicated. Twenty-nine percent knew of *C. difficile* before the survey, with 4% reporting a personal history of CDAD. Eight percent of patients reported a friend or family member who had suffered from the illness. Nine percent reported a personal history of chronic diarrhea.

Fifty-six percent of respondents reported a history of CAM use (such as acupuncture, Ayurvedic medicine, colonics, chiropractic medicine, homeopathy, or traditional Chinese

Table 1 Demographics of survey participants

Sites	
VA clinic	50% (133/267)
Faculty group practice	28% (75/267)
Public hospital	22% (59/267)
Male	65% (170/260)
English as primary language	88% (229/261)
Race (self-identified)	
White	54% (139/256)
Black	23% (59/256)
Asian	7.8% (20/256)
Other	14% (38/256)
Education	
Did not complete high school	7.5% (20/266)
High school	26% (68/266)
Vocational school	4.5% (12/266)
College	40% (105/266)
Graduate school	23% (61/266)
Income (K/year)	
<25	40% (94/238)
25-49	27% (63/238)
50-74	18% (42/238)
75-99	5.9% (14/238)
>100	11% (24/238)
Have children	62% (160/264)

K, US\$1000

medicine). Thirty-two percent of respondents reported current or prior use of probiotics, half through pill formulations and half through yogurts. Of those using probiotics, 5% did so as therapy for chronic diarrhea and 26% for overall health.

On univariate analysis, subjects with children and those with at least a university degree were more likely to agree to FMT (81% vs. 69%, $P=0.04$; 81% vs. 68%, $P=0.03$, respectively). Other factors, including a history of chronic diarrhea, use of CAM or probiotics, or prior experience with *C. difficile* infection, were not found to be significantly associated with FMT acceptability. There was a trend towards willingness to undergo FMT among those who were married versus unmarried (85% vs. 73%, $P=0.06$).

On multivariable analysis, we accounted for variables found to be significant at a $P<0.10$ level on univariate analysis; these included having children, being married, and having at least a college level education. In addition, we accounted for first or second hand experience with *C. difficile* infection in our model. Again, respondents with children and those with college degrees or higher were more likely to accept FMT (odds ratio [OR] 2.11, 95% confidence interval [CI] 1.02-4.35, $P=0.04$; OR 2.27, 1.11-4.60, $P=0.02$, respectively) (Table 2).

Our survey, which included a brief primer on FMT delivery modalities, also evaluated which modalities would be preferred

by patients. When asked to rank FMT delivery by nasogastric tube (NGT), enema, or colonoscopy, 71% of respondents ranked colonoscopy as the most acceptable vehicle for stool transplant, while NGT was the least preferred.

We then evaluated possible sources of the negative perceptions of FMT. Disease transmission was the most commonly cited concern (30%, 72/242). Other concerns included fear of the delivery procedure required for FMT (21%, 50/242) and the “dirty/unsanitary” perception of FMT (22%, 53/241). The success rate of the fecal transplant was the least selected concern (9.1%) (Fig. 1).

Discussion

FMT is an effective treatment for recurrent CDAD [15,16]. However, as with other procedures, such as screening colonoscopies, effectiveness may be tempered by patient acceptance [27]. There are currently few studies in the literature that evaluate patient perceptions of this emerging therapy. Our study expands upon this literature in both the number and breadth of the patients evaluated, as it was conducted across clinic sites for 3 distinct hospitals that together serve patients from a large range of socioeconomic, educational, and cultural backgrounds. Furthermore, we explored the factors that motivate acceptance or rejection of this therapy.

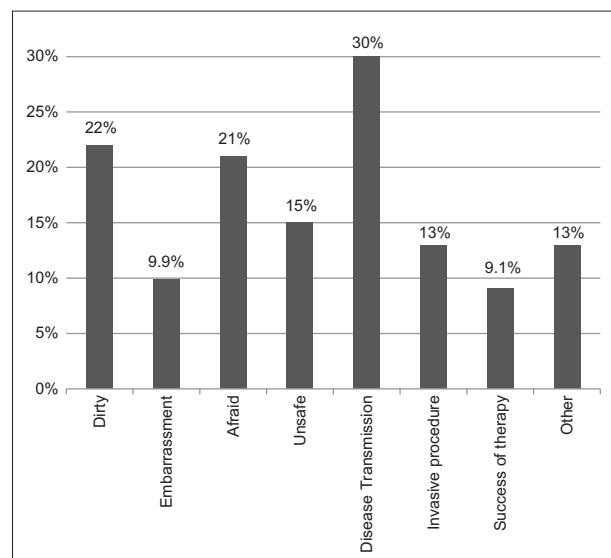
Our results show that, despite its inherently unappealing aspects, most patients are open to FMT as a therapeutic option for recurrent CDAD. This is similar to the findings of Kahn *et al* [29], who published the first study investigating patient attitudes towards FMT, evaluating it in the context of treating ulcerative colitis (UC). Using focus groups, the investigators interviewed 15 adults with UC and 7 parents of children with UC and found them willing to pursue FMT for themselves or their child as an adjunct to standard UC treatments. Interestingly, in another study of UC patients ($n=95$) by Kahn *et al* [26], the majority were willing to consider FMT despite satisfactory disease control with their current conventional treatments. In fact, patients identified safety and efficacy as the most important factors in choosing FMT as a therapeutic option, followed by the need for surgery and their physician's recommendation. As expected, patients with previous hospitalizations for UC and severe disease showed a greater interest in FMT. In our study, FMT efficacy was the least selected concern regarding the therapy. While this may be appropriate regarding FMT for CDAD indications, it is worth noting that early efficacy data on FMT for other diseases, while promising, are far more modest [28-30]. In line with such findings, at the time of this writing, the Federal Drug Administration is exercising enforcement discretion regarding Investigational New Drug (IND) applications for the clinical use of FMT for *C. difficile* not responding to standard therapies [31]. However, an IND is required for all other indications.

Also in 2012, Zipursky *et al* [25] utilized structured surveys, including hypothetical case scenarios, to investigate perceptions of FMT for recurrent CDAD in general medicine patients, the majority of whom had not suffered from CDAD

Table 2 Logistic regression analyses of variables affecting FMT acceptability

Willingness to undergo FMT	Univariate odds ratio (P-value, 95%CI)	Multivariable odds ratio (P-value, 95%CI)
Respondents with children	1.95 (P=0.04, 1.02-3.69)	2.11 (P=0.04, 1.02-4.35)
Married	2.04 (P=0.07, 0.95-4.39)	1.54 (P=0.30, 0.68-3.46)
College or graduate education	2.08 (P=0.03, 1.09-3.95)	2.27 (P=0.02, 1.11-4.60)
Experience with <i>C. difficile</i> *	1.57 (P=0.22, 0.758-3.24)	1.48 (P=0.32, 0.68-3.22)

*Either personally or through a friend or relative. While *Clostridium difficile* (*C. difficile*) experience was found to have a P value > 0.10 on univariate analysis, it was included in our multivariable regression analysis because of its presumed influence on FMT acceptability
FMT, fecal microbiota transplantation; CI, confidence interval

**Figure 1** Percentage of patients expressing concerns about FMT perceptions

or had the procedure previously. In this single-center study, the majority of subjects were white (93.5%) and female (70%). In contrast, our respondents included 23% black, 27% Hispanic, and 7.8% Asian patients, reflecting our large metropolitan environment. Our study was also predominantly male (65%). Regardless of the cultural differences between the two study populations, as well as the growing use of FMT, both studies indicate a lack of knowledge about FMT in the community, with only approximately 10% of respondents being aware of the therapy prior to survey completion. In addition, both studies found that a majority of individuals would undergo the procedure if medically indicated. Thus, despite the differences in sex and ethnicity distributions, patients' perceptions of stool transplantation are comparable.

Our findings further provide interesting insight into the potential factors that may influence patient acceptance of fecal transplant. On univariate and multivariable analyses, having children was a significant predictor for accepting FMT. It is possible that patients with children are more likely to embrace a treatment that is inherently unappealing in nature because of their drive to provide for their family. This hypothesis is further supported by our results showing a trend toward accepting FMT among those married versus unmarried. A similar

impact of familial relationships on the acceptance of medical procedures has also been found in the colon cancer screening literature [32-35]. For example, Kotwal *et al* found higher screening colonoscopy rates among married versus unmarried men. Also, husbands were more likely to obtain colonoscopies if they described their wives as happy with their marriage, more highly educated, and more supportive [35].

In our study, at least 63% of patients had university or graduate degrees. This level of education was found to be a significant predictor of FMT acceptance on univariate and multivariable analyses, suggesting that education and, presumably greater health literacy, plays an important role in FMT acceptance. Each of the prior studies of FMT acceptability also identified a positive correlation between higher education level and increased acceptance rates. Prior studies have also shown that knowledge of alternative medicine is correlated with the level of education [36,37]. While the majority of study respondents (56%) had personal experience with using probiotics or CAM, the use of such therapies did not correlate with FMT acceptance in our study.

One of the barriers to FMT uptake is the "yuck factor" associated with internalizing a filthy product. Though our study respondents were concerned that the administered stool was "dirty" (22%) and feared the procedure (21%), the most common patient concern was about disease transmission (30%). While the current literature does not support any significant disease transmission in FMTs [38], transmission of currently unrecognized infectious agents remains a possibility and is an important area for continued research.

Consideration must also be given to the mechanism of donor stool delivery. Our findings suggest a preference for colonoscopy as the most acceptable vehicle for stool transplant and NGT as the least acceptable. However, there are still practical barriers to these delivery modalities as they are invasive, unpleasant, and have the potential for complications [15]. Studies exploring more esthetically appealing, less invasive and easier methods for administration of FMT are ongoing. In a small pilot study (n=20), Youngster *et al* demonstrated 90% clinical resolution of recurrent CDAD after oral administration of frozen capsules of fecal material from unrelated donors [39]. There were no serious or unexpected adverse events. This new FMT delivery modality may help promote the availability of FMT, as it eliminates the need for patients and medical providers to handle stool suspensions and obviates the need for a gastrointestinal procedure.

Finally, another barrier to the widespread utilization of FMT to treat complicated CDAD is apprehension amongst physicians [40]. While not addressed in our study, investigation into physician attitudes reveals a lack of knowledge about the procedure itself, a misperception about patient attitudes toward FMT, and an aversion for handling stool during the treatment, with up to 29% of physicians reporting it was unappealing enough to prevent them from offering this therapy despite positive reported data [41].

Our study has some limitations. Since the survey was only distributed in English, it is difficult to draw conclusions on the views of immigrant patient populations with potential language barriers receiving healthcare in the United States. In addition, the education level and literacy of our patients may have affected their ability to fully complete and understand a somewhat lengthy study survey. Those who had difficulties reading or understanding English, regardless of reason, may have had difficulties understanding certain questions. This may have contributed to the unanswered questions on the survey, though some questions were left unanswered because of time limitations. Finally, our surveys only evaluated patients' attitudes; they did not assess physicians' attitudes toward FMT and their possible contribution to the barriers against FMT utilization.

In conclusion, FMT is an effective treatment modality for recurrent CDAD and may have significant application in other major diseases, including metabolic syndrome, inflammatory bowel disease, and other autoimmune conditions. Despite limited prior knowledge of FMT and concerns about safety, patients are receptive to the procedure, highlighting a role for shared decision-making when considering this emerging therapy. Attitudes toward FMT are modifiable barriers to

the wide-scale use of this therapy in the CDAD treatment armamentarium. Furthermore, advancements in the delivery method, such as encapsulation of donor stool, may further improve FMT's safety and acceptability.

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Summary Box

What is already known:

- Fecal microbiota transplantation (FMT) is an emerging, effective therapy for recurrent *Clostridium difficile* infection
- Patients who have previously failed traditional therapies and try FMT exhibit a cure rate of approximately 90%
- Despite its effectiveness, some patients are reluctant to accept FMT treatment

What the new findings are:

- In this study, most patients had no prior knowledge of FMT, but were receptive to the procedure
- Having children and higher education levels were significant predictors for FMT acceptance
- Our findings suggest that barriers to FMT utilization may be overcome with counseling about safety concerns

- colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012;**107**:1079-1087.
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